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EXAMINER

DADIO, S

ART UNIT

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MORGAN & FINNEGAN
345 PARK AVENUE
NEW YORK, NY 10154

1808

DATE MAILED:

10/19/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS This application has been examined Responsive to communication filed on 7/10/95 This action is made final.A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892.
2. Notice of Draftsman's Patent Drawing Review, PTO-948.
3. Notice of Art Cited by Applicant, PTO-1449.
4. Notice of Informal Patent Application, PTO-152.
5. Information on How to Effect Drawing Changes, PTO-1474.
6.

Part II SUMMARY OF ACTION

1. Claims 1 - 23 are pending in the application.Of the above, claims 14 - 21 are withdrawn from consideration.2. Claims _____ have been cancelled.3. Claims _____ are allowed.4. Claims 1 - 13 and 22 - 23 are rejected.5. Claims _____ are objected to.6. Claims _____ are subject to restriction or election requirement.7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.8. Formal drawings are required in response to this Office action.9. The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are acceptable; not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).10. The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been approved by the examiner; disapproved by the examiner (see explanation).11. The proposed drawing correction, filed _____, has been approved; disapproved (see explanation).12. Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has been received not been received been filed in parent application, serial no. _____; filed on _____.13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.14. Other

Applicant's election with traverse of Group I, claims 1-13 and 22-23, in the response filed on July 10, 1995 is acknowledged. The traversal is on the ground(s) that "applicants believe it would not be unduly burdensome for the Examiner to perform art searches directed to Groups I-III simultaneously." This argument is not found persuasive because it would indeed be an undue burden upon the Office and the Examiner to search more than one invention in the same application. The Examiner has established, in the Office action mailed on April 6, 1995, that Groups I-III are independent and distinct. The mere fact that two inventions may be classified in the same class does not provide a sound basis for arguing a lack of undue burden. Groups I, II and III all require an independent search, especially with regard to the non-patented literature searches. Accordingly it **would be** unduly burdensome for the Examiner to perform art searches directed to Groups I-III simultaneously.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-23 are currently pending in the instant application. Claims 14-21 are withdrawn from consideration as being drawn to non-elected subject matter. Accordingly, claims 1-13 and 22-23 have been examined on the merits.

Claims 1-13 and 22-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite for reciting a preamble which indicates that the claim is drawn to "[a] method of producing a population of dendritic cell **precursors** from proliferating cell cultures" (emphasis added) when the steps of the method actually indicate the

production of **mature** dendritic cells. See step (c) of claim 1. Also, it is unclear as to whether or not such cells are actually be produced from "proliferating cultures" because the steps do not indicate a positive recitation of such proliferation nor do the steps indicate that the cultures are proliferating at any particular time throughout the process.

5 Claim 1 is rendered vague and indefinite because the recitation of step (b) is awkward in structure and thus causes confusion in the claim. Applicants may consider drafting the step in the following manner: "culturing said tissue source on a substrate and in a culture medium to produce proliferating dendritic cell precursors; wherein said culture medium comprises GM-CSF and another factor which inhibits the proliferation or maturation of non-dendritic cell precursors, 10 thereby increasing the proportion of dendritic cell precursors in the culture."

Claims 2 and 4-5 are rejected for lacking proper antecedent basis for "said agent."

It appears that claim 7 contains a typographical error wherein the claim recites the term "comprise" instead of "comprises." Appropriate correction is required to rectify this minor informality.

15 Claim 13 is rendered vague and indefinite because it is unclear if the "one growth factor selected from the group consisting of TNF-[alpha], G-CSF, IL-1 and IL-3" is the other "factor" referred to in claim 1 which inhibits the proliferation or maturation of non-dendritic cell precursors or if this "one growth factor" is in addition to the "GM-CSF and another growth factor."

20 Claim 22 is rejected for not being grammatically correct. Each claim should begin with an article. Accordingly, the claim should recite "[t]he dendritic cells." Furthermore, the

dendritic cells are not "prepared according to the method of claim 1," rather they are being "produced by the method of claim 1."

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

5 A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10 The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

15 A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

20 Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

25 This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C.

§ 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-5 and 10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Markowicz et al.

Markowicz et al. teach a method of producing a population of dendritic cells. The method comprises providing a population of cells from human peripheral blood which comprises dendritic cells. The dendritic cells were then cultured in microwells containing supplemented RPMI-1640 medium, 10% heat-inactivated human serum and 100 U/ml of GM-SCF. Markowicz et al. further teach that the culture medium could additionally be supplemented with IL-4.

Accordingly, the claims would have been anticipated by one of ordinary skill in the art at the time the claimed invention was made.

Claim 22 is rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Markowicz et al.

Markowicz et al., relied upon for the reasons discussed *supra*, teach the production of dendritic cells.

The Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether or not applicants' cells differ and, if so, to what extent, from the cells discussed in the references. Accordingly, in as much as the examiner has established that the prior art cells, which are obtained from the same source and produced by the same method as that claimed, she has reasonably demonstrated a reasonable likelihood/possibility that the compared cells are either identical or sufficiently similar that whatever differences exist are not patentably significant. Therefore, the burden of establishing non-obviousness by objective

evidence shifted to applicants.

Accordingly, the claimed invention would have been at least *prima facie* obvious, if not anticipated, to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

5 Claims 6 and 11-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Markowicz et al. as applied to claims 1-5 and 10 above, and further in view of Jakoby et al.

Markowicz et al., relied upon for the reasons discussed *supra*, teach utilization of 100 U/ml of GM-CSF and IL-4. Markowicz et al. differs from the claimed invention by not specifically indicating the exact concentration level of IL-4 utilized and also by teaching the 10 utilization of a slightly less concentration level of GM-CSF from that which is specifically claimed. However, it is well known in the art to adjust the concentration level of culture medium additives in order to optimize the experimental conditions for the particular cell type being cultured. Jakoby et al., on pages 75-77, teach that it is well known in the art of cell culture to "tailor media" in order to optimize the experimental conditions. Each culture system 15 requires examination of the particular conditions that are best for the type of cell being studied by the investigator. Furthermore, each component of the system, identified as result-effective variables, has its well recognized advantages for the purpose of optimizing the experimental conditions. This type of optimizing experimental conditions is well within the purview of the skilled artisan and is deemed a matter of routine experimentation.

20 Accordingly, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of

sufficient, clear and convincing evidence to the contrary.

Claims 7 and 13 are rejected under 35 U.S.C. § 103 as being unpatentable over Markowicz et al. as applied to claims 1-5 and 10 above, and further in view of Koch et al.

Markowicz et al. differs from claim 8 by not specifically teaching that the culture medium
5 may further comprise TNF-alpha.

Koch et al teach that new insight into the biology of dendritic cells (DC) came from studies of murine epidermal Langerhans cells (LC) *in vitro*. Koch et al. indicate that such studies have suggested that LC in the skin and DC in other non-lymphoid tissues represent precursors or immature elements of the dendritic cell system. Koch et al. teaches that the addition of TNF-
10 alpha to murine epidermal Langerhans cells in culture allows such cells to maintain their viability. Therefore, in view of the teachings of Koch et al., one of ordinary skill in the art would have a reasonable expectation of success in maintaining viability of dendritic cells when TNF-alpha is added to a dendritic cell culture. Accordingly, one of ordinary skill in the art would have had a reasonable expectation of success in adding TNF-alpha to the dendritic cell
15 culture of Markowicz et al. As decided in In re O'Farrel, 7 USPQ 2d 1673 (Fed. Cir. 1988), obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law
20 nonobvious. In re Merck & Co., 800 F.2d at 1098, 231 USPQ at 380; Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1461, 221 USPQ

481, 488 (Fed. Cir. 1984); In re Papesch, 315 F.2d 381, 386-387, 137 USPQ 43, 47-48 (CCPA 1963). For obviousness under 35 U.S.C. 103, all that is required is a reasonable expectation of success. In re Longi, 759 F.2d 887, 897, 225 USPQ 645, 651-652 (Fed. Cir. 1985); In re Clinton, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976).

5 In conclusion, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 8-9 and 23 are rejected under 35 U.S.C. § 103 as being unpatentable over Markowicz et al. as applied to claims 1-5 and 10 above, and further in view of Voorhis et al or
10 Ruley et al.

Markowicz et al. differs from claims 8-9 and 23 by adding 10% heat-inactivated human serum as opposed to 1-15% fetal calf serum or 5% cord blood serum. However, Voorhis et al teach that human dendritic cells may be cultured in 5-10% fetal calf serum. Furthermore, it is well known in the animal cell culture field to utilize cord blood serum in animal cell cultures.

15 See, e.g., Ruley et al., U.S. Patent No. 5,364,783, column 22, lines 21-27. Therefore it is deemed merely a matter of judicious selection on the part of the skilled artisan to utilize fetal calf serum or cord blood serum as opposed to human serum. Additionally, it is well known in the art to utilize anywhere from 1-20% of serum in animal cell cultures. Utilization of a particular concentration within that range is deemed merely a matter of routine optimization which is well 20 within the purview of the skilled artisan.

Accordingly, the claimed invention would have been *prima facie* obvious to one of

ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 1-6, 8-9, 13 and 22 are rejected under 35 U.S.C. § 103 as being unpatentable over Hueffler et al. taken with Sallusto et al.

5 Hueffler et al. teach that murine epidermal Langerhans cells represent an important model for dendritic cells, such as dendritic cells derived from bone marrow. Hueffler et al. teach that Langerhans cells (dendritic precursor cells) may be produced into potent immunostimulatory dendritic cells (mature dendritic cells) by culturing such cells in a RPMI-1640 medium supplemented with 10% FCS, GM-CSF and IL-1.

10 Hueffler et al. differs from the claimed invention by not including IL-4 in the medium. However, Sallusto et al. teach a method of culturing human dendritic cells obtained from peripheral blood in a RPMI-1640-10% FCS medium supplemented with 50ng/ml GM-CSF and 1000 U/ml IL-4. Sallusto et al. teach that the combination of GM-CSF with IL-4 provided the best conditions for the generation of cells with the characteristic phenotype and functional properties of dendritic cells (page 1110, results section). In view of the advantages in culturing the dendritic cells in both GM-CSF and IL-4 as taught by Sallusto et al., it would have been obvious to one of ordinary skill in the art to add IL-4 to the culture medium containing GM-CSF in the method as taught by Hueffler et al.

20 Accordingly, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 10-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Hueffler et al. taken with Sallusto et al. as applied to claims 1-6, 8-9, 13 and 22 above, and further in view of Jakoby et al.

The combination of Hueffler et al. taken with Sallusto et al., relied upon for the reasons discussed *supra*, teach utilization of GM-CSF and IL-4. These references differ from the claimed invention by not specifically indicating the exact concentration level of GM-CSF which is specifically claimed. However, it is well known in the art to adjust the concentration level of culture medium additives in order to optimize the experimental conditions for the particular cell type being cultured. Jakoby et al., on pages 75-77, teach that it is well known in the art of cell culture to "tailor media" in order to optimize the experimental conditions. Each culture system requires examination of the particular conditions that are best for the type of cell being studied by the investigator. Furthermore, each component of the system, identified as result-effective variables, has its well recognized advantages for the purpose of optimizing the experimental conditions. This type of optimizing experimental conditions is well within the purview of the skilled artisan and is deemed a matter of routine experimentation.

Accordingly, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 7 and 13 are rejected under 35 U.S.C. § 103 as being unpatentable over Hueffler et al. taken with Sallusto et al. as applied to claims 1-6, 8-9, 13 and 22 above, and further in view of Koch et al.

The combination of Hueffler et al. taken with Sallusto et al. differs from claim 8 by not specifically teaching that the culture medium may further comprise TNF-alpha.

Koch et al teach that new insight into the biology of dendritic cells (DC) came from studies of murine epidermal Langerhans cells (LC) *in vitro*. Koch et al. indicate that such studies have suggested that LC in the skin and DC in other non-lymphoid tissues represent precursors or immature elements of the dendritic cell system. Koch et al. teaches that the addition of TNF-alpha to murine epidermal Langerhans cells in culture allows such cells to maintain their viability. Therefore, in view of the teachings of Koch et al., one of ordinary skill in the art would have a reasonable expectation of success in maintaining viability of dendritic cells when TNF-alpha is added to a dendritic cell culture. Accordingly, one of ordinary skill in the art would have had a reasonable expectation of success in adding TNF-alpha to the dendritic cell culture of the primary references. As decided in In re O'Farrel, 7 USPQ 2d 1673 (Fed. Cir. 1988), obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. In re Merck & Co., 800 F.2d at 1098, 231 USPQ at 380; Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1461, 221 USPQ 481, 488 (Fed. Cir. 1984); In re Papesch, 315 F.2d 381, 386-387, 137 USPQ 43, 15 47-48 (CCPA 1963). For obviousness under 35 U.S.C. 103, all that is required is a reasonable expectation of success. In re Longi, 759 F.2d 887, 897, 225 USPQ 645, 651-652 (Fed. Cir. 20 20)

1985); In re Clinton, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976).

In conclusion, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

5 Claim 23 is rejected under 35 U.S.C. § 103 as being unpatentable over Hueffler et al. taken with Sallusto et al. as applied to claims 1-6, 8-9, 13 and 22 above, and further in view of Ruley et al.

The combination of Hueffler et al. taken with Sallusto et al. differs from claim 23 by adding 10% fetal calf serum as opposed to 5% cord blood serum. However, Ruley et al., U.S. 10 Patent No. 5,364,783, column 22, lines 21-27 teaches that use of cord blood serum in animal cell cultures is well known in the art. Therefore it is deemed merely a matter of judicious selection on the part of the skilled artisan to utilize fetal calf serum or cord blood serum. Additionally, it is well known in the art to utilize anywhere from 1-20% of serum in animal cell cultures. Utilization of a particular concentration within that range is deemed merely a matter of routine 15 optimization which is well within the purview of the skilled artisan.

Accordingly, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

No claim is allowed.

20 The remaining references listed on the enclosed PTO-892 are cited to further show the state of the art at the time the claimed invention was made.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Susan M. Dadio whose telephone number is (703) 308-2392.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Susan M. Dadio
October 16, 1995

10


MICHAEL G. WITSHYN
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10-6